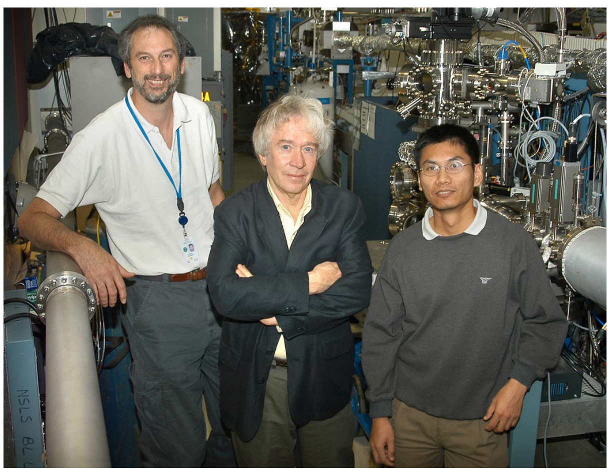
Setting the Stage to Find Drugs Against SARS

UPTON, NY - Scientists at the U.S. Department of Energy's Brookhaven National Laboratory have set the stage for the rapid identification of compounds to fight against severe acquired respiratory syndrome (SARS), the atypical pneumonia responsible for about 800 deaths worldwide since first recognized in late 2002. Researchers from Brookhaven's biology department and the National Synchrotron Light Source (NSLS) characterized a component of the virus that will be the target of new anti-SARS virus drugs. The results were published online by *Biochemistry* on November 17, 2006.



(From left) William McGrath, Wally Mangel, and Lin Yang

"Although vaccines against viruses are very effective, vaccines for viruses that mutate rapidly – such as the viruses that cause SARS, AIDS, and bird flu – are much more difficult to obtain," said Brookhaven biologist Walter Mangel, the lead author of the paper. "Even if a vaccine is available, antiviral agents are important in stopping the spread of highly infectious viruses. If antiviral agents for SARS had been available, they could have been used to contain the outbreak to the initial site of the infection."

The researchers studied the SARS main proteinase, an enzyme used by the virus during infection to cut newly made viral proteins into gene-sized, functioning pieces. If the proteinase is prevented from working, the virus infection is aborted. Previous studies have revealed that the proteinase is inactive when in the form of single molecules. But once two of those molecules bind together to make what is called a dimer, the enzyme becomes active and is able to play its role in SARS virus reproduction. The challenge for researchers, and the focus of the Brookhaven study, was to determine the concentration at which individual proteinase molecules form active dimers. Knowing this concentration, for which estimates at other laboratories have varied greatly, would allow researchers to search for anti-SARS drugs more efficiently by ensuring that the proteinase used in tests is initially in its active form.

Using three different scientific techniques, including x-ray scattering at the NSLS, the Brookhaven researchers obtained almost identical values for this concentration. Now that this crucial value has been narrowed down to a precise range, researchers can focus on finding compounds that bind to the active form of the enzyme.

"Targets for antiviral drugs must be carefully chosen such that binding to it prevents the virus from reproducing," Mangel said. "Viral proteinases are excellent targets for antiviral drugs. One reason so many people are surviving the AIDS epidemic is the effectiveness of drugs targeted to the proteinase of human immunodeficiency virus (HIV)."

One way to obtain compounds that bind to a proteinase is via high-throughput screening. Chemical libraries containing tens of thousands of small compounds are available that can be searched for effective drugs against various diseases. Small amounts of a target, e.g., an active viral proteinase, are placed in tiny wells in a plate, and a different compound from the library is added to each well.

To determine whether a compound binds to and inhibits the proteinase, an additional molecule is added that changes color in the presence of an active proteinase. Wells that don't show a color change therefore contain compounds that inhibit the proteinase, and could be effective antiviral agents. Earlier this year, Mangel's research group published a procedure on the synthesis of a new compound that changes color in the presence of the active form of the SARS main proteinase.

However, for this screening process to work, the SARS proteinase inserted into the wells has to be active to begin with. Knowing the concentration range for dimer formation will therefore help researchers in their search for a compound to stop the virus. "Now that the stage is set, high-throughput screening can begin," Mangel said. "Hopefully, it will yield an antiviral agent that can be stockpiled before a virulent strain of the virus reappears."

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— Kendra Snyder